REMARKS

This paper is in response to the Office action mailed on August 8, 2006. A one-month extension of time accompanies this Amendment.

I. Status of the Claims

Claims 1-3, 6-19, 21, 23, 24, 26, and 27 are pending.

II Amendments to the Claims

Claim 1 has been amended to incorporate the feature of claim 5. Claim 5 had been canceled, and Claim 18 has been amended to correct a word-processing error.

No new matter has been added to the claims by virtue of the amendments presented herein.

III. Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 5 under 35 U.S.C. §112, second paragraph. Specifically, the Examiner has asserted that claim 5 is indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. This rejection is traversed in view of the following remarks and arguments.

Although claim 5 has been canceled, the language of claim 5 has been incorporated into claim 1; the remarks which follow therefore now apply to claim 1 as amended.

In turning to claim 1, the claim recites the following: *"... wherein said conjugate is absent non-covalent bonds"*.

As the Examiner is aware, 35 U.S.C. §112, second paragraph, requires that the scope of the claims be clear to a hypothetical person possessing ordinary skill in the art. That is to say, the claims should meet the threshold requirements of clarity and precision. In reviewing claim 1, it can be seen that, indeed, on its face, the scope of the claim is clear. As stated, the claim reflects a conjugate that fails to possess one or more non-covalent bonds. The meaning of a "non-covalent bond" is clear to one of skill in the chemical arts, and refers to a bonding interaction between molecules or portions of molecules that is non-covalent in nature. As indicated by the language of the claim itself, such bonds are absent from the conjugate as a

whole. Thus, neither the peptide portion, the polymer portion, or any other portion of the conjugate possess a non-covalent bond. It is submitted that no further clarification or amendment to the claim is required, and that claim 1 in its present form meets the standards of clarity and precision under 35 U.S.C. §112, second paragraph.

Withdrawal of this ground of rejection is therefore respectfully requested.

III. Prior Art Rejections: Rejections Under 35 U.S.C. §103

A. GROUNDS OF REJECTION.

The Examiner has rejected claims 1-3, 5-19, 21, 23, 26, and 27 under 35 U.S.C. §103(a) as unpatentable over Delgado, et al., and Wu, et al. Specifically, it is the Examiner's position that it would have been obvious at the time of the invention to PEGylate biphalin, and that further, one would have a reasonable expectation of success to modify the PEG moiety to extend blood-brain barrier (BBB) transport. The Examiner has further asserted that it would have been obvious to PEGylate, followed by conjugation of the PEG to OX26/streptavidin for improved pharmacokinetics and BBB transport.

This rejection is respectfully traversed for the reasons which follow.

B. THE INVENTION

The present invention is directed to polymer conjugates capable *per se* of transport across the blood brain barrier. A conjugate of the invention is characterized as either biphalin or DPDPE, covalently linked to a water-soluble polymer (specific polymers are recited in Claim 1). Further, the conjugate is absent noncovalent bonds. The invention is surprising since, prior to the invention, it was believed that large hydrophilic polymers such as PEG, when attached to a peptide capable of crossing the BBB, would interfere with the transport of such peptide across the BBB. Moreover, it was further believed that such covalent attachment would impair the interaction between the peptide and its receptor.

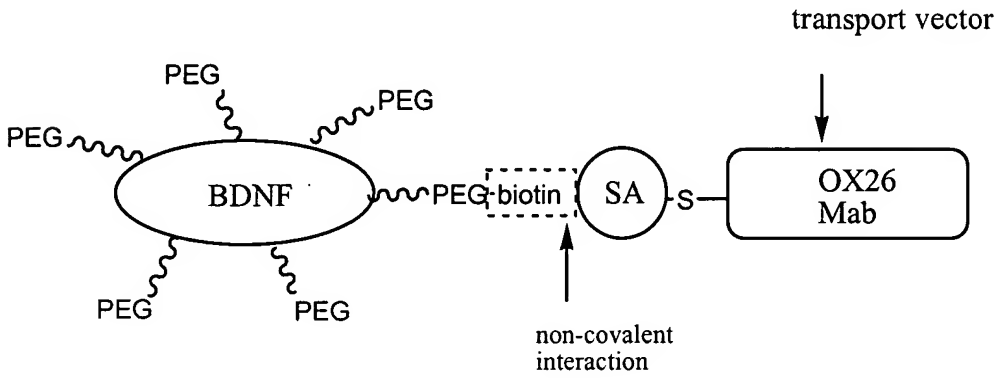
C. CITED ART

Delgado, et al. Delgado is a 1992 review article describing several PEG-modified proteins, their pharmacological and chemical properties (antigenicity, renal clearance,

bioactivity, etc.) in various systems, methods of synthesis and analyses, and the like.

Nowhere does Delgado suggest a biphalin or a DPDPE PEG conjugate, let alone such a conjugate capable of administration to the bloodstream and transport across the BBB, and having an analgesic effect.

Wu et al. Wu describes modification of brain-derived neurotrophic factor (BDNF) to provide a conjugate capable of transport across the BBB upon peripheral administration.



The structure of the Wu conjugate is provided pictorially above. As can be seen, the Wu conjugate employs the combined use of PEGylation technology (e.g., the PEG chains), chimeric peptide technology (e.g., the OX26 Mab), and avidin-biotin technology (e.g., the biotin-streptavidin, SA) (p. 254, column 2).

Wu further describes the function of each component of the BDNF conjugate. Wu describes the PEG chains as preventing rapid uptake of the protein by peripheral tissues, while the OX26 Mab functions as the transport vector which provides transport of the conjugate through the BBB, owing to high concentrations of the rat transferring receptor on the brain capillary endothelium. Conjugation of the PEG segment to the OX26 Mab is accomplished via a biotin/streptavidin complex. As Wu clearly describes, transport of the above three-component conjugate is facilitated by the OX26 Mab transport vector – not by the PEG.

Nowhere does Wu describe or even remotely suggest preparing a BDNF conjugate where BDNF is conjugated merely to PEG, for transport across the blood brain barrier or for any other purpose. Indeed, on page 257, column 1, Wu states that in order to demonstrate therapeutic

efficacy, BDNF *must be* (i) conjugated to a BBB drug delivery system (i.e., OX26 Mab), and (ii) PEGylated to improve plasma pharmacokinetics. Thus, to modify Wu to arrive at a conjugate of the present invention would be to go against the very teachings of Wu – by eliminating a feature described by Wu as essential to the invention (i.e., the transport vector).

Specifically, the conjugates of the claimed invention are not only capable of crossing the BBB, but are capable of doing do absent noncovalent bonds of the sort critical to Wu. In contrast, as shown above, Wu requires the presence of biotin-streptavidin to connect the PEG and the transport vector in the resulting conjugate, where the biotin-streptavidin system is one of the strongest *noncovalent* biological interactions known. In fact, Wu states on page 257, column 2, that monobiotinylation and placement of biotin are *critical factors* involved in enabling transport of BDNF across the BBB (second and third full paragraphs). The claimed invention clearly lacks this feature.

Finally, Wu is directed to neutrophic factors such as BDNF, a protein produced from a nucleotide sequence over 4000 nucleotides in length. Such compounds, i.e, neutrophic factors, on both structural and pharmacological grounds, are distinct from the small peptides of the present invention. Biphalin is a dimer made up of eight amino acids, while DPDPE possesses the structure, Tyr-D-Pen-Gly-Phe-D-Pen (where Pen refers to penicillamine). Nowhere does Wu suggest small peptides of the sort presently claimed, nor does Wu suggest anything other than a combination of PEGylation and attachment of a drug delivery system such as OX26 Mab to BDNF to provide transport across the BBB.

In sum, nowhere does Wu suggest, when considered either singly or in combination with Delgado, a polymer conjugate of the type recited in the Applicant's claims.

D. ARGUMENT

In determining whether a claimed invention is obvious, the following tenants must be adhered to:

i. The claimed invention must be considered as a whole;

ii. The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; and

iii. The references must be viewed without the benefit of hindsight afforded by the claimed invention or accompanying specification.

A prior art references must be considered in its entirety, i.e., as a whole, *including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983).*

Both the invention as claimed and the cited art are characterized in the preceding sections. As can be seen, the prior art at best teaches a conjugate of BDNF that is capable of transport across the BBB and having optimized plasma pharmacokinetics. The BDNF conjugate of the prior art possesses PEG chains attached thereto, as well as a single PEG chain attached to a OX26 Mab transport moiety via a biotin-streptavidin (BioS) system. Nowhere does Wu suggest modifying the conjugate described therein to remove either the BioS system, and/or the OX26 Mab moiety, since to do so would result in elimination of two of the very features stated to be critical to the conjugate described therein. Moreover, to do so, based upon the teachings of Wu, would result in a conjugate incapable of transport across the BBB – that is to say, which goes against the very point of Wu! Further, nowhere does Wu provide the slightest suggestion for replacing BDNF with either biphalin or DPDPE.

In sum, Wu, when considered as a whole and in combination with Delgado, fails not only to suggest a conjugate of the type presently claimed, but also fails to provide the slightest motivation to modify the teachings therein to arrive at a conjugate of the type recited in claims 1-3, 6-19, 21, 23, 24, 26, and 27.

In sum, the references relied upon by the Examiner fail to render obvious the claimed invention as recited in the claims currently pending. In view of the above, it is submitted that the claims currently pending in the application are non-obvious over the art of record. Withdrawal of the rejection of the claims under 35 U.S.C. §103(a) is therefore respectfully requested.

IV. Conclusion

Commencement of prosecution on the merits in this case is thus respectfully requested.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 493-3400.

Respectfully submitted,

Date: November 17, 2006 By: _____

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